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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,121	10/23/2000	Debra G. Gilbertson	00-53	2404

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EXAMINER	
ANGELL, JON E	
ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,121	GILBERTSON, DEBRA G.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,11-13,15 and 17-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,11-13,15 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 5/6/03, as Paper No. 12. Claims 1-6, 9, 11-13, 15 and 17-25 are currently pending in the application and are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Double Patenting

3. Claims 1-6, 9, 11-13, 15 and 17-25 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41, 42 and 46-54 of copending of copending Application No. 10/139,583, for the reasons of record.

4. Applicants have elected to defer action on this rejection, but have indicated that in the event the '583 Application issues as a patent and the rejection remains in the present case, an appropriate terminal disclaimer will be filed.

Claim Rejections - 35 USC § 112

1. Claims 1-6, 9, 11-13, 15 and 17-25 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting cell proliferation caused by zvegf3 activity in a mammal comprising administering to the mammal a composition comprising a zvegf3 antagonist in

combination with a pharmaceutically acceptable delivery vehicle, in an amount sufficient to reduce zvegf3 activity, wherein said zvegf3 antagonist is an antibody that specifically binds to a dimeric protein having two polypeptide chains, wherein each of the polypeptide chains consists of a sequence of amino acid residues selected from the group set forth (see claim 1), whereby administering said composition to said mammal results in inhibition of cell proliferation caused by zvegf3;

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Response to Arguments

2. Applicant's arguments filed 5/6/03 as Paper No. 12 have been fully considered but they are not persuasive.

3. Applicants argue that the claims have been rejected as a group and has not addressed the patentability of individual claims or groups of claims and the applicants argue that the claims do not stand or fall together. (See p. 2, lines 15-21 of Paper No. 12)

4. In response, it is acknowledged that the claims do not stand or fall together; however, the claims have been examined individually. It is respectfully pointed out that fibrosis is disorder characterized by increased cell proliferation, increased extracellular matrix production and increased stellate cell activation. It is acknowledged that reducing cell proliferation, reducing extracellular matrix formation and reducing stellate cell activation are all different from each other and do not necessarily encompass treating fibrosis. However, many of the issues regarding treating fibrosis overlap with the issues associate with decreasing cell proliferation, decreasing

extracellular matrix formation and decreasing stellate cell activation in a subject. Therefore, although all of the claims have been rejected, they were examined individually and the claims do not stand or fall together.

5. Applicants argue that the claims appear to be based on a characterization alternative to methods for reducing cell proliferation or extracellular matrix production and methods for reducing stellate cell activation. Applicants point to the previous Office Action which indicates, "it is unlikely that administration of zvegf3 antibody alone would be able to halt cell proliferation, extracellular matrix formation and stellate cell activation associated with fibrosis" and "it is unlikely that any single agent will effectively stop renal fibrosis". Applicants contend that the claims "do not require halting or effectively stopping any disease or related process" and point out that the terms "treat and "treatment" are defined in the specification as "to denote therapeutic and prophylactic interventions that favorably alter a pathological state" and includes "procedures that moderate or reverse the progression of, reduce the severity of, prevent, or cure a disease." (Emphasis added; see p. 2, last paragraph).

6. In response, it is respectfully pointed out that the claims do require halting or stopping a disease or related process. First, the definition of "treat" and "treatment" encompasses prophylactic intervention, as well preventing and curing a disease. In order for a method to be a prophylactic intervention, or for a method to prevent or cure a disease it is essential that the method halts or effectively stops a disease or related process. Cell proliferation, extracellular matrix production and stellate cell activation are all processes related to fibrosis. Although the applicants contend that "the claims do not require a complete inhibition or halting of stellate cell activation or any other process", the claims drawn to treating (i.e. preventing or curing) fibrosis

encompass completely inhibiting and halting the processes related to fibrosis, including stellate cell activation, cell proliferation and extracellular matrix formation. Therefore, the claims have been properly interpreted and the rejection has been appropriately applied.

7. Regarding the breadth of the claims, the applicants appear contend that the claims are not very broad and indicate their view of the varying scopes of the claims. Furthermore, Applicants contend that the Office has failed to differentiate among the 20 pending claims and have used the same broad-brush rejection to all claims, apparently disregarding the cited limitations. (See p. 3, first two paragraphs).

8. In response, the Examiner acknowledges the varying scope of the claims; however, the claims are very broad. For instance, although the claims are drawn to different methods such as reducing cell proliferation or extracellular matrix formation and reducing stellate cell activation using a specific antibody and in specific cell types the claims encompass treating any cell hyperproliferative disorder, any extracellular matrix disorder associated with an overabundance of extracellular matrix and any activated stellate cell disorder wherein the disorders can be caused by **any mechanism** (i.e., the disorders can be caused by mechanisms independent of zvegf3). Therefore, the claims are very broad. Furthermore, as indicated above, many of the issues between the claims overlap. For instance, although methods of reducing stellate cell activation are separate from methods of treating fibrosis, treating fibrosis encompasses treating any process associated with fibrosis, including stellate cell activation and increased cell proliferation and increased extracellular matrix formation. Therefore, problems associated with treating fibrosis and fibrosis related processes can and do overlap.

9. Applicants argue that each of the cell types encompassed by claim 2 is known to express PDGF receptors which respond to PDGFs and zvegf3 has been shown to exert its mitogenic activity by binding to and activating PDGF receptors, one of skill in the art would reasonably conclude that a zvegf3 antagonist could be used to reduce proliferation of these cells. (See p. 3, third paragraph).

10. In response, it is respectfully pointed out that the previous Office Action indicated that the prior art has recognized a mutant PDGF receptor which is constitutively active, even in the absence of ligand (see p. 6 of the previous Office Action which discusses the Kitamura reference). It is pointed out that the claims encompass reducing cell proliferation or extracellular matrix production wherein the cell proliferation may be due to any cause, including a mutant PDGF receptor such as the one described by Kitamura. Because Kitamura indicates that the mutant PDGF receptor is constitutively active (even in the absence of ligand), it is highly unlikely (without evidence to the contrary) that any PDGF ligand antagonist (such as a zvegf3 antagonist) could reduce the cell proliferation associated with the constitutively active PDGF receptor.

11. Applicants argue that zvegf3 induces stellate cell activation and TGF-beta production, therefore it would be reasonable to conclude that the antibody to zvegf3 could be used to reduce extracellular matrix production and fibroproliferative disorders of the liver and kidney including liver fibrosis and kidney fibrosis. (See p. 4).

12. In response, it is pointed out that the claims encompass reducing stellate cell activation or extracellular matrix production or liver or kidney fibrosis due to any cause. It is unlikely, absent evidence to the contrary, that the zvegf3 antibody could reduce stellate cell activation or

extracellular matrix production in cells comprising the constitutively active PDGF receptor mutant described by Kitamura, because the mutant receptor is always active regardless of ligand (i.e., zvegf3) binding. If an antagonist is unlikely to reduce stellate cell activation/extracellular matrix formation it is also unlikely to reduce fibroproliferative disorders or any other disorder associated with stellate cell activation/extracellular matrix formation.

13. Regarding the state of the prior art and unpredictability of the art, Applicants contend that the rejection cannot be sustained in view of a correct reading of the claims. Applicants contend that the claims are drawn to "reducing" and "treating" certain processes and the specification teaches the use of zvegf3 antibodies in combination with inhibitors of other mitogenic factors. Furthermore, Applicants argue that the claims recite, "comprising administration to the mammal a composition comprising a zvegf3 antagonist". Applicants argue, "Hence, the claims include combination therapies" and "None of the claims requires that the zvegf3 antagonist alone provide complete cessation or reversal of any process or condition" (see p. 5).

14. In response, it is respectfully pointed out the claims do not explicitly indicate composition comprising a zvegf3 antagonist and another inhibitor in combination. It appears that the Applicants are reading limitations of the specification into the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the claims encompass administrating any composition comprising a zvegf3 antagonist; however, there is no specific limitation that the composition must comprise another inhibitor. Therefor it is not inappropriate to interpret the claims as encompassing administrating a composition comprising a zvegf3 antagonist as the only functional inhibitor. Therefore, the

claims have been read correctly and the rejection is appropriate.

15. Applicants also argue that the presence of inoperative embodiments does not necessarily render a claim nonenabled, as indicated in MPEP 2164.08(b).

16. In response, it is respectfully pointed out that MPEP 2164.08(b) indicates,

> "The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).
> Although, typically, inoperative embodiments are excluded by language in a claim (e.g., preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. In re Angstadt, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976).
> However, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971)." (Emphasis added)

In the instant case the claims are very broad and drawn to methods of reducing cell proliferation or extracellular matrix production, methods of reducing stellate cell activation, and methods of treating fibroproliferative disorders such as fibrosis wherein said proliferation, production, activation and disorder are caused by **any mechanism,** including mechanisms not yet identified. The prior art (as mentioned before) indicates that cell proliferation/extracellular matrix production, stellate cell activation, and fibroproliferative disorders can be caused by different mechanisms including, as one example, a constitutively active PDGF receptor. Therefore, it is clear that embodiments exist which are not enabled. Although the claims may

encompass nonenabled embodiments, in the instant case one of skill in the art would not be able to determine which embodiments conceived but not yet made, would be inoperative or operative without expenditure of undue effort.

Regarding the quantity of experimentation required, Applicants argue that the specification has disclosed conventional assays which could be used "to determine the ability of the antibodies to reduce the effects of zvegf3 on target cells" (see p. 7, last paragraph). It is respectfully pointed out that the pending rejection is a scope of enablement rejection wherein the claims have been deemed enabled to the extent that the methods read on reducing the effects of zvegf3 on target cells. However, the claims are not enabled for the full scope of the claims which encompasses reducing cell proliferation caused by any mechanism, treating (which includes preventing based on the definition of "treatment" in the specification) fibroproliferative disorders, such as fibrosis wherein said disorder is caused by any mechanism including mechanisms independent of zvegf3 activity, etc. For the reasons of record, it has been concluded that an undue amount of experimentation would be required in order to use the claimed methods to the full scope encompassed by the claims.

In summary, the claims have been rejected for not being enabled for the full scope of the claims. The claims are enabled for:

A method for inhibiting cell proliferation caused by zvegf3 activity in a mammal comprising administering to the mammal a composition comprising a zvegf3 antagonist in combination with a pharmaceutically acceptable delivery vehicle, in an amount sufficient to reduce zvegf3 activity, wherein said zvegf3 antagonist is an antibody that specifically binds to a dimeric protein having two polypeptide chains, wherein each of the polypeptide chains consists

of a sequence of amino acid residues selected from the group set forth (see claim 1), whereby administration of said composition to said mammal results in inhibition of cell proliferation caused by zvegf3;

However, the claims are not enabled for reducing cell proliferative disorders/extracellular matrix production caused by mechanisms other than zvegf3, reducing stellate cell activation, and treating/preventing fibrotic disorders because it is clear that the methods would not work to the full scope encompassed by the claims and undue experimentation would be required in order to practice (i.e., use) the claimed method to the full scope encompassed by the claims.

Allowable Subject Matter

It is respectfully pointed out that amending the claims such that the claims are drawn to:

A method for inhibiting cell proliferation caused by zvegf3 activity in a mammal comprising administering to the mammal a composition comprising a zvegf3 antagonist in combination with a pharmaceutically acceptable delivery vehicle, in an amount sufficient to reduce zvegf3 activity, wherein said zvegf3 antagonist is an antibody that specifically binds to a dimeric protein having two polypeptide chains, wherein each of the polypeptide chains consists of a sequence of amino acid residues selected from the group set forth in presently pending claim 1, whereby administering said composition to said mammal results in inhibiting cell proliferation caused by zvegf3;

would obviate the rejection and the claims would be allowable.

Conclusion

No claim is allowed.

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
July 12, 2003